REMARKS

Claims 12-27 are pending, with claims 12-15 and 23-27 presently under examination. Claims 16-22 were previously withdrawn from consideration as being directed to a non-elected invention. Applicants request cancellation of claim 23 without prejudice or disclaimer. Applicants submit that the pending claims are in condition for allowance and respectfully request notice to that effect.

Applicants have reviewed the Final Office Action mailed May 16, 2007, and respectfully traverse all grounds of rejections for the reasons that follow.

Rejection Under 35 U.S.C. §112, First Paragraph

Claims 12 and 23-27 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly lacking enablement for "sodium channel inhibiting substance[s]" other than tolperisone, eperisone, silperisone, riluzole, propafenone, lidocaine, flecainide, and metixen. The Examiner states that the rejected claims are overbroad "due to plethora of compounds having characteristics of a sodium channel inhibiting substance." According to the Examiner, undue experimentation would be required to practice the full scope of the invention and that the claims require an exhaustive search for the embodiments suitable to practice the claimed invention.

Applicants submit that in cases pertaining to the enablement requirement of 35 U.S.C. §112, first paragraph, the Court of Appeals for the Federal Circuit has held that an enablement analysis begins with the disclosure in the specification. (*Sitrick v. Dreamworks* at page 10, CAFC, Case No. 2007-1174, decided Feb. 1, 2008). Further, the enablement requirement is satisfied when one skilled in the art, after reading the specification, could practice the claimed invention without undue experimentation. *AK Steel Corp. v. Sollac*, 344 F.3d 1234, 1238-39 (Fed. Cir. 2003) at 1244. Pertinent to the biochemical field, the Court has long held that as long as the means for carrying out the invention is fully disclosed, there is no absolute requirement to include working examples in the specification and that the absence of such examples does not *ipso facto* render a patent invalid for lack of enablement. *In re Stephens,* 529 F.2d 1343, 188 USPQ 659 (CCPA 1976). Applicants respectfully submit that the specification sufficiently exemplifies enablement of the full scope of the claims for the reasons set forth below.

The Examiner has acknowledged that the specification describes tolperisone, eperisone, silperisone, riluzole, propafenone, lidocaine, flecainide, and metixen as *suitable* sodium channel inhibitors. (*see* Office Action mailed September 21, 2006, at page 4, lines 7-9) It is submitted that these examples provide a sufficient number of exemplary compounds to satisfy the enablement requirement because the skilled person would reasonably associate the term "sodium channel-inhibiting substance[s]" with compounds which possess sodium channel inhibiting capacity. For instance, tolperisone, eperisone and silperisone, although sharing structural similarity to one another, are of distinct chemical structure compared to the structural classes of riluzole, propafenone, lidocaine, flecainide, and metixen. Applicants respectfully assert that recognition of the *functionality* of a given compound enables the skilled person to determine sodium channel inhibiting substances useful in the practice of invention as claimed. Given this understanding, the skilled person would be able to practice the present invention with compounds other than those recited in the claims as long as the compounds possessed sodium channel inhibiting character.

In addition, throughout the specification, as well as several references contained within the specification, provide the general state of what is commonly known in the art including, for example, description of methods of measuring sodium channel inhibiting capacity. See page 1, lines 35-39 through page 2, lines 1-3 of the application as filed wherein, the contribution of sodium channel inhibiting compounds, such as propofol, to muscle relaxing activity is described. In this instance, based on the teachings of the specification, the skilled person would be able to ascertain that such muscle relaxing activity would be associated with inhibition of sodium channels. Further, page 3, lines 11 to 20, describe the inhibition of voltage dependent sodium channels by compounds such as tolperisone and lidocaine. In addition, several references of record *(see,* Kennel et al. *J. Neurol. Sci.* 2000; 180: 55-61, De Luca et al. *J. Pharmacol. Exp. Ther.* 1997; 282: 93-100, Duranti et al. *Eur J. Med. Chem.* 2000; 35: 147-156 and Rosenfeld et al. *Ann. Neurol.* 1997; 42: 811-814 at page 2 of the specification as filed) describe the sodium channel inhibiting character of compounds other than tolperisone and its analogs. Kennel et al., for example, cited on page 2, line 10 of the application as filed, teach that riluzole has been shown to significantly retard the progress of the functional parameters connected to muscle strength by effectively inhibiting sodium ion channels.

With respect to the level of experimentation required to practice the invention and the Examiner's assertion that the scope of the instant application would require "an exhaustive search for the embodiments suitable to practice the claimed invention," Applicants respectfully submit that while it is appropriate to recognize variability in determining the scope of invention, determination of what is needed to support claims to biological subject matter depends on a variety of factors including 1) knowledge in the particular field, 2) the extent and content of the prior art, 3) the maturity of the science or technology, and 4) the predictability of the aspect at issue. *Capon v. Eshhar*, 76 U.S.P.Q.2d 1078, 1084, 418 F.3d 1349, at 1356 (Fed. Cir. 2005).

Although routine testing might be required to determine the sodium channel-inhibiting capacity associated with a given compound, such testing would not rise to the level of undue experimentation because such methods were well known in the art at the time of the application. This is evidenced in the specification wherein the claimed substances inhibited sodium channels sufficient to elicit a physiological response, for example, by decreasing muscle tone (Haeseler, page 3, lines 4-5 of the application as filed), inhibiting neurotransmitter release (Obrenovitch, page 2, lines 4-8 of the application as filed) or by decreasing hyper-excitability in skeletal muscles (Duranti, page 2, lines 18-21 of the published application). Accordingly, an exhaustive degree of experimentation would not be required to practice the invention.

In particular, Applicants respectfully direct the Examiner's attention to Novalies-Li, *et al., Eur. J. Pharmacol.,* 168:299-305 (1989), referenced on page 3, lines 31-35, of the application as filed, which is enclosed herewith, which describes measurement of voltage-dependent ion flows using voltage clamp experiments. Page 300, second paragraph of Novalies-Li, *et al*, discusses a voltage clamp system with two microelectrodes filled with 2 M CsCl and 1 M TEA, wherein membrane currents were recorded during study of eperisone, tolperisone and isoperisone. Further, the calcium current is described to have been separated by suppressing the sodium and potassium currents in a solution titrated to pH 7.4. Using similar experimental methods, During and Koppenhofer, *Gen. Physiol. Biophys.* 20:157-73 (2001), referenced on page 3, line 35-39 of the application as filed showed that tolperisone analogs reduced sodium ion permeability. In particular, Applicants respectfully direct the Examiner's attention to page 159, paragraphs 1-3 of During and Koppenhofer, wherein sodium inactivation curves were measured "by the well known two-pulse protocol (Frankenhaeuser, 1959)."

Therefore, although routine testing might be necessary in determining the sodium channel inhibiting character of a given compound, any experimentation would not be undue, since methods to test for sodium channel inhibiting character were well known at the time of the application as evidenced by the teachings of the specification and references therein.

Regarding the alleged unpredictability of pharmacological activity of therapeutic combinations of the invention, it is not necessary that every permutation within a generally operable invention be effective in order for an inventor to obtain a generic claim, provided that the effect is sufficiently demonstrated to characterize the generic invention. *See*, e.g., *In re Angstadt*, 537 F.2d 498, 504 (CCPA 1976). Accordingly, generic inventions are not *per se* invalid because success for each possible iteration is not assured. *Capon*, at 1357.

The claims presently under rejection represent more than a mere germ of an idea, the specification supplies the novel aspects of the invention, and identification of substances which alleviate neuropathic pain, in part, by inhibiting sodium ion channels (e.g., page 6, lines 15-39). In the instant case, the specification teaches the functionality required to practice the invention and therefore, the full scope of the claims are enabled. Further the general teachings of how the super-additive efficacy of the combination therapy of retigabine with sodium channel inhibitors presented with specific examples have been described (e.g., page 6, lines 27-31). Moreover, standardized assays which measure calculated and predicted ion channel activity, are well known in the art as illustrated by the cited references. And while such procedures involve some level of technical manipulation, because such methods and steps are routinely used in the art, such procedures do not rise to the level of undue experimentation. (See, e.g., *Johns Hopkins University v. Cellpro, Inc.*, 47 U.S.P.Q.2d 1705, 152 F.3d 1342 (Fed. Cir. 1998), wherein the court stated that experimentation does not constitute undue experimentation where it is merely routine).

Therefore, Applicants submit that the claims are enabled because the specification provides appropriate guidance and prediction of function based on observed properties of the claimed combinations such that one of skill in the art could practice the invention as claimed, in the absence of undue experimentation. For these reasons, Applicants respectfully request that the rejection be Withdrawn.

Rejection Under 35 U.S.C. §112, Second Paragraph

Claims 14 and 15 stand rejected under 35 U.S.C. §112, second paragraph, as being indefinite allegedly because the term "other tolperisone analogs" is unclear.

Applicants submit that the specification, including the cited references therein, which serve as a measure of the level of skill in the art at the time the application was filed, would reasonably convey to the skilled person the metes and bounds of the rejected claims. Applicants respectfully direct the Examiner's attention to page 6, lines 15-17 and page 4, lines 10-14, of the specification as filed, wherein Applicants describe tolperisone analogs in significant detail. Applicants further submit that tolperisone analogs were well known to those skilled in the art as pointed out in the Exhibits of Applicants' previous response (filed February 15, 2007).

With respect to the Exhibits, Applicants respectfully point out that the Examiner has failed to address how the Exhibits fail to adequately articulate the level of knowledge in the art with respect to the term "other tolperisone analogs."

> In order to provide a complete application file history and to enhance the clarity of the prosecution history record, an examiner must provide clear explanations of all actions taken by the examiner during prosecution of an application. Where the applicant traverses any rejection, take note of the applicant's argument and answer the substance of it. MPEP 707.07(f)

Applicants submit that the Exhibits demonstrate that the level of knowledge and skill in the art at the time the application was filed was such that the skilled person would understand the meaning of the term "other tolperisone analogs" as recited.

With respect to any assertion that claim 14 is unclear because it includes the term "other," Applicants respectfully point out that the phrase refers to other tolperisone analogs. Hence, the plain language of the claims makes clear that other tolperisone analogs refers to tolperisone analogs other than eperisone and silperisone. Withdrawal of the rejection is respectfully requested.

Rejection Under 35 U.S.C. §103(a)

Claims 12-15 and 23-27, stand rejected under 35 U.S.C. §103(a) as being unpatentable over Rundfeldt et al. (U.S. Patent No. 6,117,900, hereafter "Rundfeldt") in view of Cai et al. (U.S. Patent No. 6,281,211, hereafter "Cai"), in further view of Applicants statements at page 1, line 25 through page 4, line 3, of the application as filed. For the reasons set forth below, it is respectfully submitted that the Examiner has not met the *prima facie* burden of articulating a reason to combine the cited references.

The Examiner bears the burden of proof in establishing a *prima facie* case of obviousness under §103. *In re Piasecki,*745 F.2d 1468, 1472 (Fed.Cir. 1984). To establish a *prima facie* case of obviousness, three basic criteria must be met: 1) a suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; 2) a reasonable expectation of success; and 3) the references must teach or suggest all the claim limitations. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991); MPEP § 2143. It is respectfully submitted that the current Office Action falls short of establishing a *prima facie* case of obviousness.

Rundfeldt is alleged to describe the administration of retigabine for treatment of neuropathic pain. The Examiner concedes that Rundfeldt fails to teach a combination therapy for such treatment but relies on Cai to cure the deficiencies of Rundfeldt. Cai is alleged to describe the use of sodium channel blockers in the treatment of neuralgia or neuropathic pain. The Examiner further alleges that Applicants statements at page 1, line 25 through page 4, line 3, of the application as filed teach the use of sodium channel inhibitors or tolperisone in normalizing or maintaining muscle tone spasticity. The Examiner concludes that it would have been obvious to one of ordinary skill to combine administration of retigabine with a sodium channel blocker because each is used for the same purpose.

Applicants submit that independent claims 12 and 15 are unobvious because the Examiner has failed to articulate reasoning as to why one skilled in the art would be motivated to combine the teachings of the cited references and arrive at the present invention. In the instant rejection, the Examiner appears to base obviousness on the grounds that the elements of the present invention were well known in the art at the time of the application. Applicants

respectfully submit that the Examiner has summarily determined that such a combination would be obvious to the skilled person but does not provide a rational underpinning as to why this would be the case. For example, on page 8 of the Office Action mailed May 16, 2007, the Examiner maintains that:

> One having ordinary skill in the art would have expected that tolperisone would behave similar as to the known sodium channel blocker lidocaine and provide therapeutic utility in the treatment of neuropathic pain through sodium channel blocking mechanism. One would have been motivated to combine these references and make the modification because they are drawn to the same technical fields (constituted with same ingredients and share common utilities), and pertinent to the problem which applicant concerns about. MPEP 2141.01(a).

There is a lack of reasoning as to why the skilled person would arrive at the present invention in light of the cited references. Absent such reasoning, Applicants submit that there is no suggestion or motivation to supporat a *prima facie* case of obviousness.

Applicants submit that there is a lack of motivation or suggestion to combine the cited references because at most, the references describe *individual* administration of the compounds described therein. In order to demonstrate a *prima facie* case of obviousness the Examiner must make a showing of how the prior art suggested making the necessary modifications to arrive at the present invention. In the instant case, none of the references cited teach a combination therapy to alleviate pain and instead, rely on individual administration to provide therapeutic benefit. For example, column 7, lines 51-53 of Rundfelt, describes administration of retigabine at 5, 10 and 20 mg/kg orally to inhibit late phase pain reactions in a dose-dependent manner. Administration occurs singly absent co-administration of additional compounds. Applicants submit that Rundfelt shows that there is no desire to combine Retigabine with another compound because it describes an effective decrease in pain reaction in study subjects following an *individual* dose of retigabine. (*e.g., see,* column 7, lines 56-64 of Rundfeldt) Hence, the skilled person would not be motivated to combine the teachings of Rundfeldt with the cited references because Rundfeldt demonstrates effective treatment absent co-administration of additional compounds. Accordingly, Applicants submit that Rundfeldt fails to suggest the necessary modifications which would allow the skilled person to arrive at the present invention.

Further, Cai fails to cure the deficiencies of Rundfeldt because Cai is directed to individual administration of semicarbazides as sodium channel blockers to alleviate pain and neuronal damage. Applicants submit that similar to Rundfeldt, Cai also shows no desirability to combine a sodium channel blocker with another compound because Cai is directed to individual administration of sodium channel blockers and thus, provides the skilled person with no motivation to combine therapeutic agents as claimed in the presently claimed. Further, there is no teaching or suggestion that the compounds of Cai would benefit from a co-administration of additional compounds (i.e., retigabine) to improve therapeutic benefit. For example, column 2, at lines 58-67 and column 3, lines 1-12, of Cai describe the intended aspects associated with the invention. In particular, column 3, line 5 of Cai, describe the invention as providing "a pharmaceutical *composition* useful for treating disorders responsive to the blockade of sodium channels..." Therefore, the skilled artisan would recognize the teachings of Cai to represent reasonable evidence that effective pain treatment would be achieved by an individual dose administration of the disclosed semicarbazides.

In light of the therapeutic and super-additive benefit described in the present specification, Applicants submit that the skilled person would have no reasonable expectation of success in arriving at the present invention in light of the cited references, because at most, the references describe individual administration. It is also noted that the observed super-additive effect of combining potassium channel openers such as retigabine with sodium channel inhibitors was an unexpected benefit of the method of treatment as claimed and a benefit which the skilled person would not have anticipated given the teachings of the cited references. (*see, e.g.,* page 6, lines 27-31 of the application as filed.) Since the teachings of Rundfeldt would not result in a combination method for treatment of pain when combined with the teachings of Cai and the Applicants cited description, one skilled in the art would not have an expectation of success because the invention as claimed could not be achieved in view of such teachings, especially in the view of the unpredictability of the art, as admitted by the Examiner.

Applicants submit that because there is no reasonable expectation of success, and there is no motivation to combine the cited references, the Examiner has failed to present a *prima facie* case of obviousness as applied to independent claims 12 and 15. Claims 13, 14, 16-22 and 24-27

depend from claims 12 and 15 are therefore patentable for at least the same reasons. Applicants request withdrawal of these rejections.

CONCLUSION

In light of the amendments and remarks herein, Applicants submit that the claims are now in condition for allowance and respectfully request a notice to this effect. The Examiner is invited to call the undersigned attorney if there are any questions.

Without addressing the merits of the rejections set forth in the Office Action mailed May 16, 2007, Applicants have canceled claim 23 without prejudice to Applicants pursuing these claims in a related application.

To the extent necessary, a petition for an extension of time under 37 C.F.R. 1.136 is hereby made. Please charge any shortage in fees due in connection with the filing of this paper, including extension of time fees, to Deposit Account 502624 and please credit any excess fees to such deposit account.

Respectfully submitted,
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